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## Phenotype Characterization of HD Intermediate Alleles in PREDICT-HD

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CONFLICT OF INTEREST

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## Abstract

**Background:** Huntington disease (HD) is a neurodegenerative disease caused by a CAG repeat expansion on chromosome 4. Pathology is associated with CAG repeat length. Prior studies examining people in the intermediate allele (IA) range found subtle differences in motor, cognitive, and behavioral domains compared to controls.

**Objective:** The purpose of this study was to examine baseline and longitudinal differences in motor, cognitive, behavioral, functional and imaging outcomes between persons with CAG repeats in four ranges: normal (< 26), intermediate (27–35), reduced penetrance (36–39), and full penetrance (> 40).

**Methods:** We examined longitudinal data from 1379 participants (280 normal [NA], 21 intermediate [IA], 88 reduced penetrance [RP], and 986 full penetrance [FP] allele ranges). We used linear mixed models to identify differences in baseline and longitudinal outcomes between groups. Three models were tested: 1) no baseline or longitudinal differences; 2) baseline differences but no longitudinal differences; and 3) baseline and longitudinal differences.

**Results:** Model 3 was the best fitting model for most outcome variables. Differences between the NA and the FP group account for the majority of significant findings. Some differences between the RP and NA groups were significant. While there were baseline and longitudinal trends of declining performance across increasing CAG repeat length groups, we found no significant differences between the NA and IA groups.

**Conclusions:** We did not find evidence to support differences in the IA group compared to the nongene-expanded controls. These findings are limited by a small IA sample size.

## Keywords

Huntington disease; intermediate alleles

## INTRODUCTION

Huntington disease (HD) is an inherited, autosomal dominant neurodegenerative disease caused by a CAG repeat expansion on chromosome 4 [1]. For people in the affected range of 36 or more CAG repeats, age of disease onset is related to length of CAG repeat, with longer CAG repeats associated with earlier age of onset [2]. HD symptoms include motor, cognitive, behavioral, and functional changes, with a formal diagnosis based on the presence of characteristic motor signs [1].

Current genetic testing guidelines define ranges for disease manifestation based on CAG repeat length: 26 = normal (NA); 27–35 = intermediate (IA); 36–39 = reduced penetrance (RP); 40 = full penetrance (FP) [3]. Persons in the RP range may not develop a formal diagnosis in their lifetimes [4]. Individuals in the IA range are highly unlikely to develop a formal diagnosis, although there are several notable case reports. Several authors present cases of persons with 27–34 CAG repeats demonstrating chorea and involuntary movements, sometimes accompanied by saccadic changes, dystonia, cognitive changes, depression, anxiety, irritability, and cortical and/or caudate atrophy [5–9].

More recently, evidence from large observational studies suggests that persons in the IA range display subtle abnormalities in motor, cognitive, and behavioral domains compared to controls. In an analysis of the Cooperative Huntington's Disease Observational Research Trial (COHORT), 50 of the 1985 participants were in the IA range and demonstrated worse saccade velocity, dystonia, and performance on the Stroop Color and Word test compared to controls [10]. In an analysis of the Prospective Huntington At Risk Observational Study (PHAROS) by Killoran et al. [11], 50 of the 983 participants were in the IA range and had significantly worse apathy and suicidal ideation than controls. The authors of that article suggest the IA range might represent prodromal HD or a behavioral subphenotype. The purpose of the current analysis was to examine baseline and longitudinal differences in motor, cognitive, behavioral, functional and imaging outcomes between persons in the IA range and persons in the NA, RP, and FP ranges who participated in the Neurobiological Predictors of Huntington's Disease (PREDICT-HD) study.

## MATERIALS AND METHODS

### Participants and data

Participants included in this analysis came from the PREDICT-HD study. PREDICT-HD is a prospective, international, 32-site study that follows persons who previously underwent testing for the HD gene expansion. Those who tested with their longest allele length  $\geq 36$  participated as gene-expanded cases and those with longest allele length  $\leq 35$  participated as control participants. A total of 1379 individuals are included in the data set: 1078 cases and 301 controls, with more than ten years of follow-up data available for some participants. All participants provided written informed consent and were treated in accordance with the ethical standards of each site's institutional review board. Inclusion criteria required independent HD genetic testing prior to entering the study, and required all individuals be age 18 and above at the time of study entry. Exclusion criteria mandated that cases must not have sufficient motor signs for a clinical HD diagnosis at study entry, no history of traumatic

brain injury or other central nervous system injury or diseases, no pacemakers or metallic implants, no prescribed use of antipsychotic or phenothiazine-derivative antiemetic medication in the past six months, and no clinical evidence of unstable medical or psychiatric illness. This dataset is ideal for exploring disease progression in HD prior to motor diagnosis due to the large sample of premanifest individuals and longitudinal data. These data may be sensitive to subtle changes that potentially begin several years before motor diagnosis.

## Measures

We selected a sample of cognitive, motor, behavioral, functional and imaging measures from the PREDICT-HD battery that have shown sensitivity to disease progression [12–17]. Measures from the Unified Huntington's Disease Rating Scale [1] include total motor score, Stroop Color and Word Test [18], and Symbol Digit Modalities Test (SDMT) [19]. Behavioral variables include the total and subscale scores from the Frontal Systems Behavioral Scale (FrSBe) [20] and the Symptom Check List 90 (SCL-90-R) [21]. Functional variables included the total scores from the Everyday Cognition (ECog) scale [22], and the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) [23]. Both participant-rated and companion-rated versions of the WHODAS and ECog are included to account for the possibility of decreased reliability of self-reported functioning resulting from disease progression [13–17]. We also included MRI measures for striatal volume processed using BRAINS image processing software [24].

## Participant stratification and analysis aims

Progression groups were defined by CAG repeat length according to American College of Medical Genetics (ACMG) and American Society of Human Genetics (ASHG) [3] guidelines as follows: NA 26, IA 27–35, RP 36–39, and FP 40. The primary aim of this analysis was to examine differences between IA individuals and the NA group, with particular attention paid to cognitive and behavioral manifestations. Based on previous studies that support a behavioral subphenotype for the IA range, our hypothesis was that IA individuals would demonstrate worse average performance compared to the NA group with respect to behavioral measures. In PREDICT-HD analyses, IA individuals are usually grouped with controls [25].

## Statistical analyses

All analyses were performed using the statistical software program R (version 3.1.2), and maximum likelihood was used throughout. First, sample sizes, measures of centrality, and measures of variability were obtained for the demographic variables age (at baseline) and years of education. Analysis of variance (ANOVA) *F*-tests were used to determine whether an overall statistically significant difference in means existed between groups. Pearson's chi-squared test was used to assess differences in gender proportion by group. Second, linear mixed models (LMMs) [26] were used for the longitudinal analysis. Each outcome of interest was analyzed separately, using the following predictors: time, group, and interaction between time and group. We included the covariates age (at baseline), years of education, and gender to control for these variables. Time was measured as duration of follow-up for all

longitudinal analyses. The intercept corresponds to the outcome measures at baseline, and the slope corresponds to the annual rate of change in the outcome.

Three models were assessed for each outcome: Model 1 = no baseline group differences or group differences over time; Model 2 = baseline group differences but no group differences over time; and Model 3 = baseline group differences and group differences over time. The Akaike information criterion (AIC) [27] was used to select the optimal model from among the three. The AIC is known for its ability to select a model that balances the two competing goals of model building: adequacy of the model fit to the observed data and model parsimony (simplicity). LMMs yield unbiased parameter estimates under the assumption that the missing data are ignorable [28]. After the optimal model was selected, *t*-tests were carried out to assess differences at baseline and over time between the IA and NA groups, RP and NA groups, and FP and NA groups.

## RESULTS

### Demographics

Our dataset consisted of 1379 participants in four ranges according to their longest CAG repeat allele: 280 were in the NA range, 21 were in the IA range, 88 were in the RP range, and 990 were in the FP range. Demographic data, including group, gender, years of education, and age are presented in Table 1. Statistical evidence at the 0.05 level concluded that there were differences in mean age at baseline and years of education between groups, with all *p*-values < 0.0001. Therefore, age (at baseline) and years of education, along with gender, were controlled for in the LMM analyses. Data on years of education were not available for one IA and four FP participants. Consistent with the female/male ratio in both the COHORT and PHAROS studies, our sample was approximately two-thirds female. Previous data indicates that more women than men complete HD genetic testing [29]. The PREDICT-HD sample consisted of individuals who had already been tested and thus our female/male ratio is representative of the population who underwent testing.

### Longitudinal analysis via LMMs

Table 2 presents results from the LMMs (estimates, *t*-test statistics, and model fit) via the process described above. Model 3 (both baseline and longitudinal differences between groups) was the best fitting model for most of the outcome variables. Model 1 (no baseline or longitudinal differences) was the best fitting model for disinhibition, and Model 2 (baseline differences but no longitudinal differences) was the best fitting model for several measures. However, there were no statistically significant differences in baseline or longitudinal outcomes between the IA and NA groups. The vast majority of significant findings were due to differences between the NA and FP groups, indicated by *t*-test results with absolute magnitude of 2 (these appear in bold in Table 2). These findings are consistent with already published data from the PREDICT-HD study [15, 16].

In order to aid in digesting the large number of results, Figure 1 provides a graphical representation of *p*-values from the statistical tests conducted in Table 2. On the *x*-axis, *p*-values are plotted separately for the differences between the three groups—IA, RP, and FP—

compared with the controls on the 31 outcome variables examined ( $y$ -axis). Baseline differences are plotted using solid lines, while longitudinal differences are plotted using dashed lines. Horizontal dashed lines are plotted at  $y = 0.05$  in order to aid in assessing significance of results. Model 1 was optimal for one outcome (FrSBe disinhibition) and this outcome is the last variable listed on the  $x$ -axis (see Figure 1 key). The dashed line for the slope disappears as variable number increases. This is due to the fact that the optimal model (selected via the AIC) for some variables did not include group differences over time. Also, as shown in Table 2 and noted above, Model 1 was the best fit for FrSBe disinhibition, (i.e., no intercept or slope comparisons available). Therefore, no points are plotted for this variable in Figure 1, which explains the gap at the final variable in Figure 1. In summary, Figure 1 provides graphical demonstration of the lack of significant differences between the IA and the NA group across all measures.

While there were no significant baseline or longitudinal differences between the IA and NA group, our data do indicate evidence of gradient effects on several measures, including behavioral measures. Gradient effects are defined by evidence of increasing impairment or dysfunction from the NA group to the FP group (these appear in italics in Table 2). For instance, if considering a cognitive measure for which higher values are indicative of cognitive impairment, a gradient effect would be said to exist if the NA group had the lowest baseline mean (slope), followed by the IA group, then the RP group, and finally the FP group. Evidence of baseline gradient effects were found for participant-rated WHODAS, TMS, Beck Depression Inventory (BDI), SCL-90 obsessive compulsive scale, SCL-90 depression subscale, SCL-90 anxiety subscale, SCL-90 hostility subscale, SCL-90 global severity index, SCL-90 positive symptom distress index, FrSBe executive subscale, and FrSBe total. Evidence of longitudinal gradient effects were found for Stroop Color and Word Test – color condition, Stroop Color and Word Test – interference condition, companion-rated WHODAS, striatal volume, SCL-90 obsessive compulsive scale, participant-rated ECog memory, and companion-rated ECog language.

Figures 2, 3, and 4 provide visual representation of the longitudinal changes in three measures with known sensitivity to changes in prodromal HD: the SDMT, TMS, and striatal volume [15]. In these visual representations, those in the IA group show patterns of change similar to those in the NA group, while those in the RP group show patterns similar to those in the FP group.

## DISCUSSION

This is the first known study to examine both baseline and longitudinal differences between IA and NA, RP, and FP allele ranges in a large sample. While we found evidence of baseline and longitudinal differences between the groups, we did not find evidence of differences between the IA group and the NA group. Most of the differences were between the FP and NA groups, with a few baseline and longitudinal differences between the RP and NA groups. Given the large number of outcome measures examined, we expected to find some significant differences between IA and NA groups, even if just by chance. Negative findings are consistent with current genetic testing guidelines that indicate persons in the IA range



are unaffected by the HD gene expansion [3]. However, it is possible that with a larger sample size of IA participants some of these differences would be significant.

Some researchers have postulated that environmental or genetic modifiers might cause some people within IA ranges to express a behavioral subphenotype, including increased depression, apathy, suicidal thoughts, suicide attempts, and history of psychiatric disease [6, 11]. We did not find evidence to support a behavioral subphenotype for the IA group in our sample, although several baseline gradient effects were found in behavioral measures, including obsession, depression, anxiety, hostility, and global severity and positive symptom distress on the SCL-90. At the same time, significant baseline differences in the RP group compared to the NA group (shown in Figure 1) included two behavioral measures, depression (BDI) and hostility (SCL-90). The RP group also showed significant changes over time in longitudinal SDMT, companion-rated WHODAS, and striatal volume compared to the NA group. This suggests that even those in the RP range who do not display motor signs required for a definitive diagnosis of symptomatic HD exhibit some of the characteristics associated with manifest HD. Gradient effects are suggestive of a toxic gain-of-function pathology in HD (i.e. pathology increases with increased CAG repeat length even if it does not meet diagnostic criteria for manifest HD). This is consistent with the findings for the RP group described above.

Longitudinal gradient effects were also present for frontal behaviors affecting executive function and total frontal behaviors score. However, the only longitudinal gradient effect for a behavioral measure that was observed was for SCL-90 obsessive compulsive scale. We did find the presence of increased baseline depression and hostility behavioral symptoms in the RP group compared to the IA and NA groups, which suggests that increased CAG length might be associated with behavioral changes even though they are not apparent in our IA sample. However, we did not find longitudinal differences between RP and NA groups on any behavioral measures.

Our data also showed longitudinal gradient effects for some cognitive outcomes (Table 2), including Stroop Color and Word Test – color and interference conditions, and participant-rated ECog memory and companion-rated ECog language. The RP group showed a decline in performance compared to the NA group over time on SDMT. There were baseline gradient effects for the participant-rated WHODAS and longitudinal gradient effects for the companion-rated WHODAS. There was a baseline gradient effect for the TMS and longitudinal gradient effect for the striatal volume. Therefore, we have evidence of gradient effects across groups in all domains: behavioral, cognitive, functional, motor, and imaging. These findings could change with larger sample sizes for the IA and RP groups since phenotype expression is likely to be heterogeneous, even in the RP range [30].

The precise mechanism of neurological damage in HD is unclear, although it likely involves multiple processes [31]. Two proposed pathways include a cumulative damage model and a one-hit model. The cumulative damage model is supported by the negative association between CAG length and age of onset. However, the one-hit model supports the phenomenon of a threshold for manifest HD at 36 CAG repeats. Although our data demonstrate gradient effects for several measures across the CAG length ranges, there still

appears to be a clear threshold for formal HD diagnosis at 36 repeats. Of course, disease pathology in HD could involve both cumulative damage and threshold effects [32], with increasing amounts of mutant protein overwhelming neuronal repair systems once it reaches a threshold accumulation [31].

Figures 2, 3, and 4 reinforce that participants in the IA group show patterns of change similar to those in the NA group, while those in the RP group show patterns similar to those in the FP group. Genetic counselors and clinicians encounter the issue of explaining the significance of CAG repeat lengths in the IA and RP ranges to individuals undergoing HD genetic testing. Indeed, subtle differences between the IA and the NA group are evident in Figures 2, 3, and 4. In Figure 2, the upward slope for performance by controls on the SDMT is indicative of practice effects [25]. The RP and FP groups show downward slopes indicative of cognitive impairment that overrides practice effects. While the IA group slope is slightly positive, it is flatter than the control group slope, which might indicate subtle cognitive changes that result in reduced ability to benefit from practice effects. In Figure 3, the slope for TMS is slightly negative, unlike the slopes for the RP and FP groups. Thus, the motor phenotype is not displayed by the IA group in our sample. Figure 4 shows that striatal volume decreases over time in all groups, which might be correlated with aging. While the slope in the IA is not significantly different from the control group, the striatal volume is slightly lower and a longitudinal gradient effect was evident in the data.

More data are needed before definitely stating that the IA range displays some of the changes associated with HD, including whether it might involve a behavioral subphenotype. We already have evidence that there are likely environmental and genetic factors that impact whether persons in the RP range develop manifest HD. Once we have more specific information regarding the factors that impact phenotype expression in the IA and RP ranges, it might become increasingly important to more accurately report the length of a person's longest CAG repeat allele. Little attention is given in the literature to the issue of inconsistent reporting of CAG repeat lengths, which occurs in up to 51% of tests [33]. The ACMG/ASHG guidelines state that acceptable error rates for CAG repeat lengths is  $\pm 2$  repeats for alleles with less than 50 repeats [3]. This error rate might not be acceptable for individuals at the edge of one of the repeat ranges. In the future, HD genetic testing might require a two-tier approach using an additional long-read sequencing platform such as PacBio [34, 35] for persons with CAG lengths in the equivocal ranges (i.e., within 2 CAG repeats of another range).

The major limitation of our findings is the small sample size of participants with CAG alleles in the IA and RP ranges compared to NA and FP groups. The 21 participants in our IA group represent 1.5% of our sample. This is not overly surprising considering that prevalence of IA in the general population is low, with estimates ranging from 1.9%–6% [36–38]. The RP group of 90 represents 6.4% of our sample. Previous studies indicate that the CAG repeat length in the general population is bimodal, with an average of 17 for those with longest alleles in the NA range and 41 in the FP range. CAG repeat lengths 28–38 are less common [11].



A caveat to our analysis when comparing behavioral results from IA analyses in the COHORT and PHAROS studies with PREDICT-HD is that these three observational studies define case and control groups differently. In PREDICT-HD, all participants know their HD gene status prior to enrollment; cases are persons who tested positive for the HD gene expansion and controls are persons who tested negative. In COHORT, participants do not have to know their gene status to enroll and controls consist of spouses or caregivers. In PHAROS, all participants are at risk for HD but do not know their gene status; cases are positive for the gene expansion and controls are negative for the gene expansion. Therefore, it is reasonable to expect that behavioral outcomes might differ between at-risk individuals who know their gene status versus those who do not. There is evidence that persons who feel as though they will cope poorly with positive results self-select to not complete HD genetic testing [39]. Furthermore, genetic testing protocols and pretest counselling might screen out individuals who are more psychologically vulnerable [40]. Therefore, our sample, which only includes persons who have chosen to undergo testing for the HD gene expansion, might not be representative of all individuals at risk for HD in terms of psychological functioning. This could explain why we found less evidence of behavioral differences between those in the IA and the NA range than the studies that included participants who are blinded to their HD gene expansion status.

## Conclusion

Our data compared baseline and longitudinal differences in cognitive, behavioral, functional, motor, and imaging outcomes across NA, IA, RP, and FP CAG range groups. We found evidence of baseline and longitudinal differences in the RP and FP groups compared to the NA group. We also found gradient effects on a number of measures across domains, supporting a cumulative damage effect for the CAG repeat expansion. On the other hand, only persons in the RP and FP ranges had outcome measure results significantly different from NA range participants, supporting a threshold phenomenon of HD pathology at 36 CAG repeats. More data are needed to accurately characterize the IA subphenotype.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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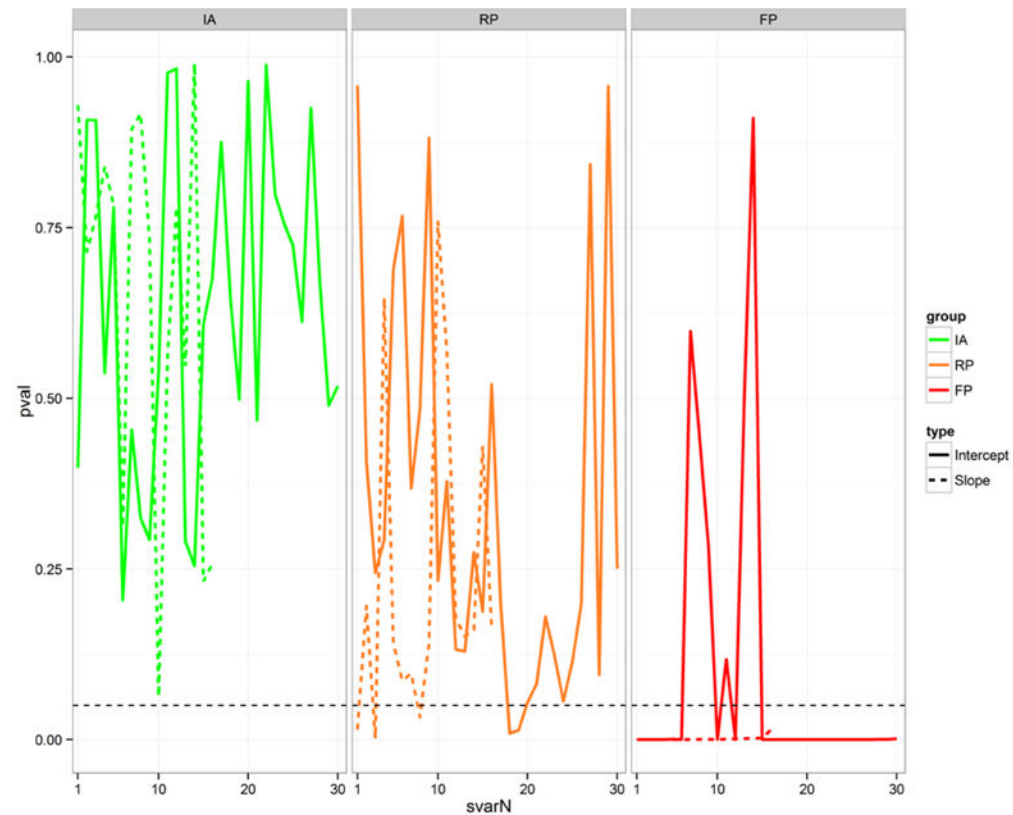
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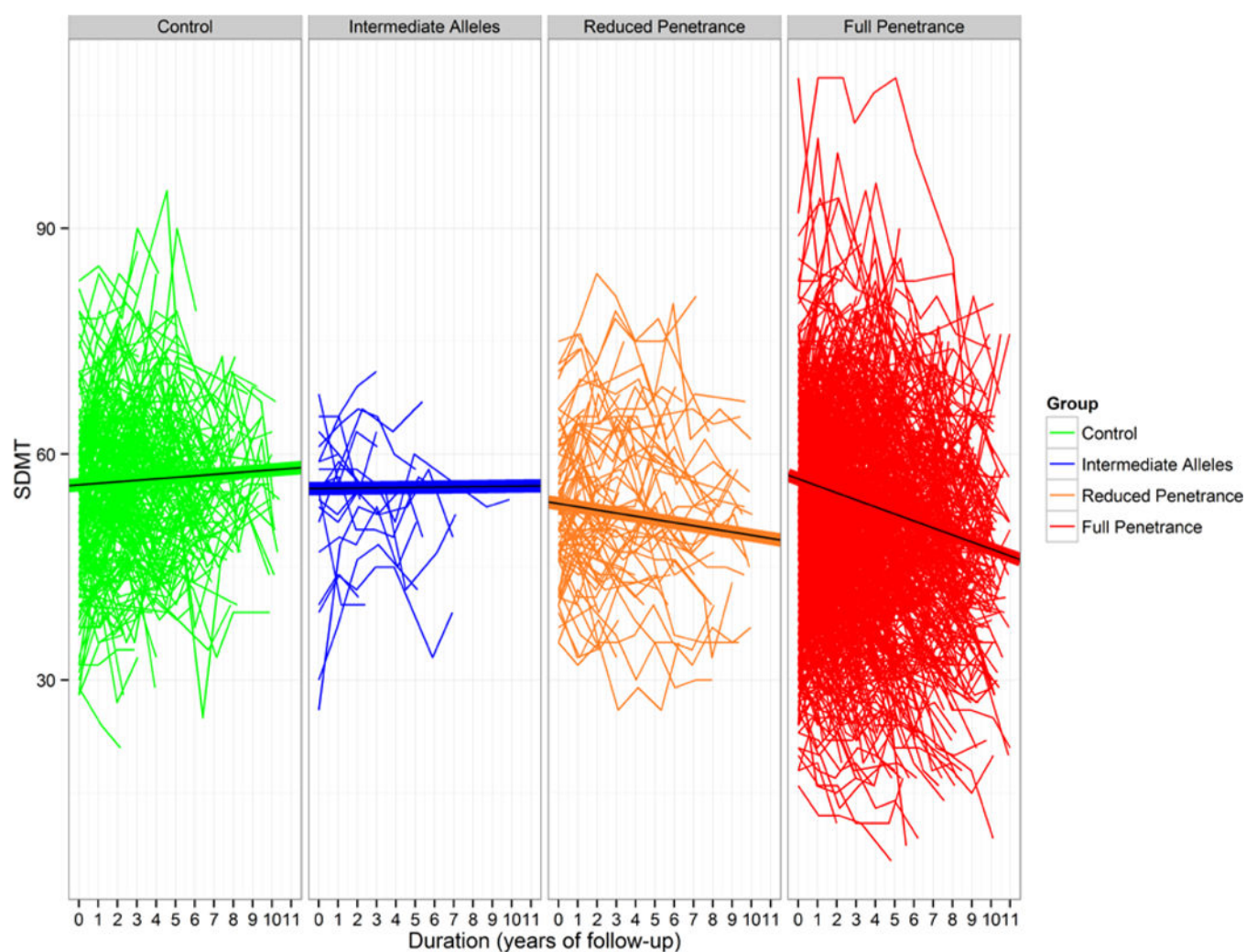


Solid lines represent tests for baseline differences and dashed lines represent tests for longitudinal differences. Key: 1 = Symbol Digit Modalities Test; 2 = total motor score of the Unified Huntington's Disease Rating Scale; 3 = Striatal; 4 = Stroop Color and Word Test – color condition; 5 = Stroop Color and Word Test – interference condition; 6 = Stroop Color and Word Test – word condition; 7 = Everyday Cognition (ECog) memory – companion rated; 8 = World Health Organization Disability Schedule (WHODAS) – companion rated; 9 = ECog language – companion rated; 10 = Frontal Systems Behavioral Scale (FrSBe) – executive subscale; 11 = ECog executive functioning; 12 = Symptom Checklist 90 (SCL-90) – obsessive compulsive subscale; 13 = ECog memory – participant rated; 14 = ECog visual spatial – companion rated; 15 = FrSBe total; 16 = SCL-90 positive symptom total; 17 = ECog language – participant rated; 18 = Beck Depression Inventory (BDI); 19 = SCL-90 – hostility subscale; 20 = FrSBe – apathy subscale; 21 = SCL-90 positive symptom distress index; 22 = SCL-90 – depression subscale; 23 = SCL-90 – Global Severity Index; 24 = SCL-90 – psychoticism; 25 = SCL-90 – anxiety subscale; 26 = WHODAS – participant rated; 27 = ECog executive functioning – participant rated; 28 = SCL-90 phobic anxiety; 29 = ECog visual spatial – participant rated; 30 = SCL-90 paranoid ideation; 31 = FrSBe disinhibition subscale.

**Fig. 1.**

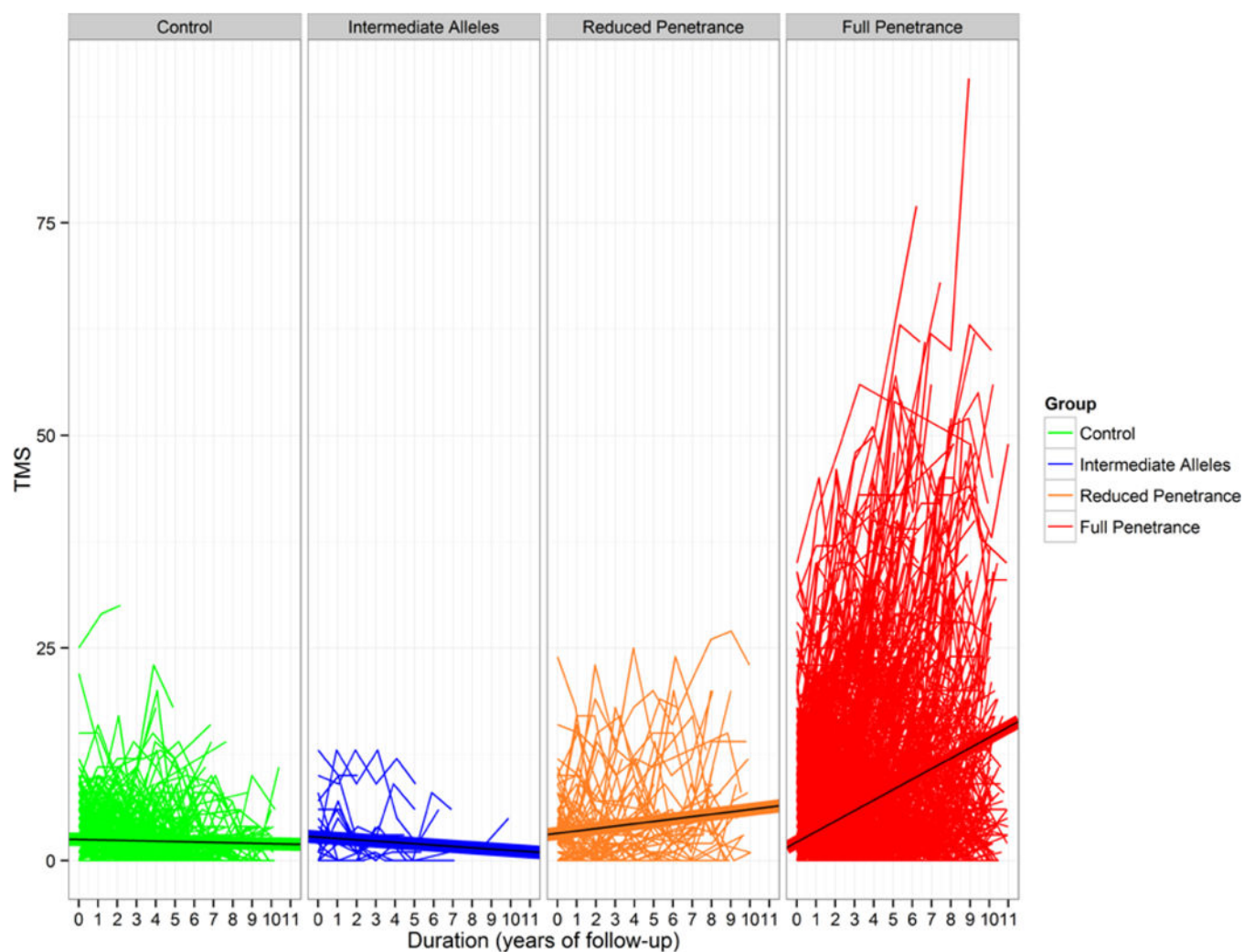
Visualization for  $p$ -values comparing intermediate (IA), reduced penetrance (RP), and full penetrance (FP) groups to controls.



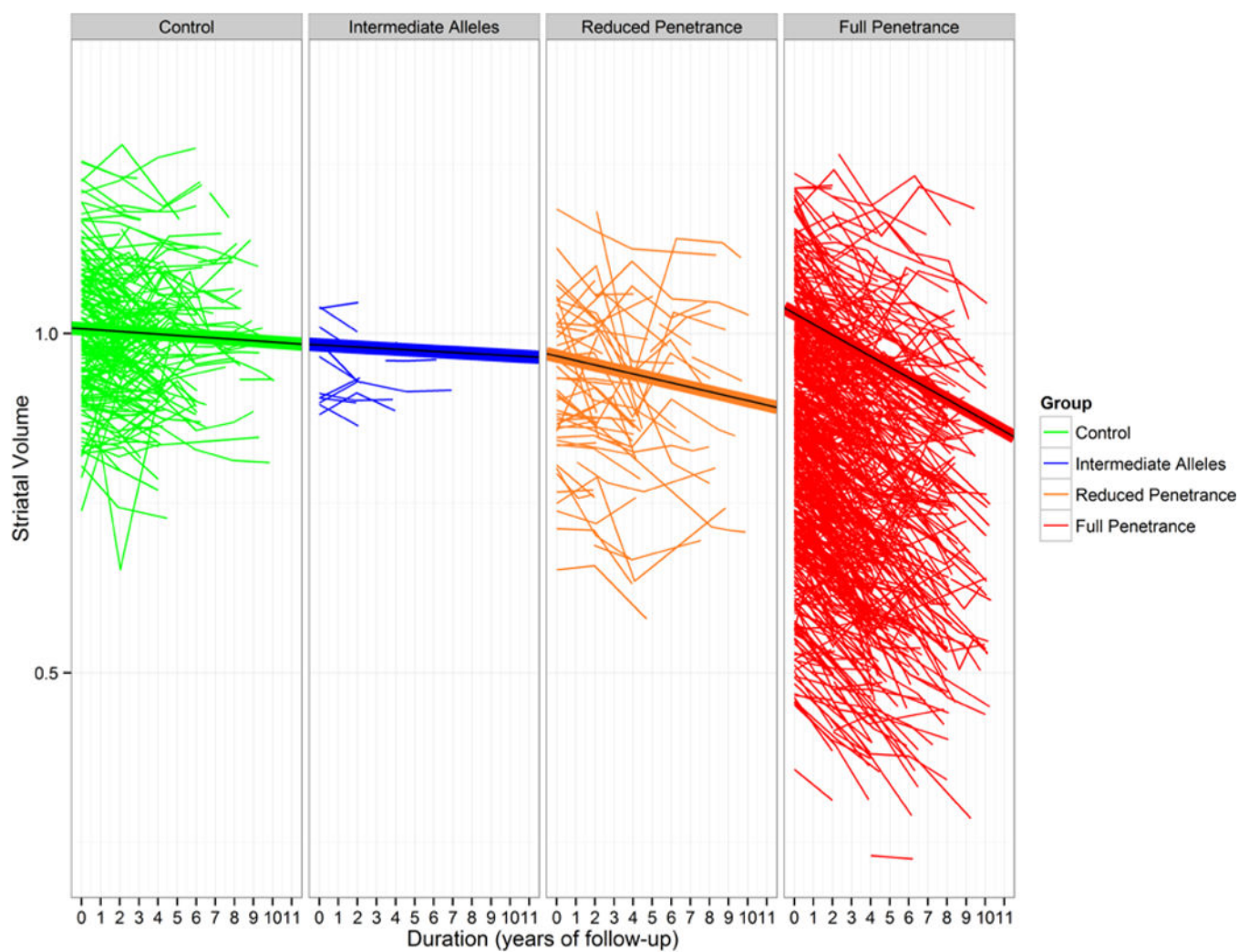


**Fig. 2.** Plots of linear trends over time by group for Symbol Digit Modalities Test (SDMT) adjusted for age, gender and education.





**Fig. 3.** Plots of linear trends over time by group for total motor score (TMS) adjusted for age, gender, and education.



**Fig. 4.** Plots of linear trends over time by group for striatal volume adjusted for age, gender and education.

**Table 1**

Demographic variables

Group	<i>n</i>	% Female	Years education mean* (SD)	Years education median [range]	<i>n</i>	Age (baseline) mean* (SD)	Age median [range]
Control	280	64	14.80 (2.59)	15.50 [8–20]	280	43.67 (11.95)	44.69 [19.15–83.73]
IA	20	65	15.55 (2.42)	16.00 [12–20]	21	47.27 (10.42)	45.05 [24.21–69.99]
RP	88	60	14.49 (2.70)	14.00 [8–20]	88	48.69 (11.45)	48.09 [20.80–75.85]
FP	986	64	14.46 (2.60)	14.00 [8–20]	990	38.99 (9.91)	38.46 [18.11–67.90]

IA = intermediate; RP = reduced penetrance; FP = full penetrance.

Table 2

Linear mixed models results table

Variable (Best model fit)	Domain	Intercepts						Slopes					
		Estimates			<i>t</i> -tests: group vs. NA			Estimates			<i>t</i> -tests: NA vs. 0, group vs. NA		
		NA	IA	RP	FP	IA	RP	FP	NA	IA	RP	FP	FP
Stroop word (3)	Cog	105.02	100.27	105.61	99.38	-1.27	0.30	-4.95	-0.07	0.51	-0.55	-1.19	-7.22
Stroop color (3)	Cog	83.76	81.90	82.09	78.82	-0.62	-1.05	-5.46	0.29	0.20	0.19	-0.76	-8.16
Stroop interference (3)	Cog	47.55	46.94	48.01	45.30	-0.28	0.40	-3.45	0.39	0.30	0.17	-0.31	-8.09
SDMT (3)	Cog	56.35	54.33	56.28	52.14	-0.84	-0.05	-5.83	0.20	0.23	-0.22	-0.73	-9.72
WHODAS (p) (3)	Func	12.80	13.30	13.50	14.28	0.51	1.28	4.68	0.21				
WHODAS (c) (3)	Func	13.44	12.07	13.95	13.77	-0.99	0.70	0.77	-0.002	0.04	0.36	0.37	3.69
TMS (3)	Motor	2.32	2.44	2.76	4.86	0.12	0.83	8.37	-0.05	-0.21	0.23	1.18	10.30
Striatum (3)	Imag	1.02	1.02	1.00	0.85	0.12	-1.16	-16.00	-0.002	-0.004	-0.009	-0.02	-13.36
BDI (3)	Beh	5.17	6.09	7.84	8.68	0.46	2.61	6.21	-0.06				
SCL-90 obsession (3)	Beh	51.01	51.07	53.53	56.44	0.02	1.51	5.71	-0.41	-0.25	-0.02	0.13	3.38
SCL-90 depression (2)	Beh	49.05	49.09	51.13	53.58	0.01	1.34	5.27	-0.11				
SCL-90 anxiety (2)	Beh	46.59	47.49	48.75	50.20	0.35	1.58	4.79	-0.12				
SCL-90 hostility (2)	Beh	48.25	49.96	51.57	52.68	0.68	2.47	5.84	-0.20				
SCL-90 phobic anxiety (2)	Beh	46.82	45.74	49.11	49.62	-0.43	1.67	3.70	0.17				
SCL-90 paranoid ideation (2)	Beh	47.38	48.64	48.58	49.31	0.65	1.15	3.29	-0.17				
SCL-90 psychoticism (2)	Beh	48.91	48.00	51.93	53.33	-0.31	1.91	5.04	-0.15				
SCL-90 global severity index (2)	Beh	48.82	49.56	51.27	53.28	0.25	1.54	5.06	-0.14				
SCL-90 positive symptom total (3)	Beh	49.64	50.73	50.53	52.86	0.42	0.64	4.13	-0.87	-1.36	-0.57	-0.58	2.44
SCL-90 positive symptom distress index (2)	Beh	46.70	48.35	48.82	50.35	0.73	1.74	5.28	-0.22				
FrSBe executive (3)	Beh	24.56	25.77	25.81	26.71	0.61	1.19	3.63	-0.25	-0.94	-0.20	0.10	3.53
FrSBe disinhibition (1)	Beh								-0.005				
FrSBe apathy (2)	Beh	11.71	11.66	12.87	13.62	-0.04	1.93	5.60	0.08				
FrSBe total (3)	Beh	55.10	57.11	57.85	59.51	0.51	1.32	3.73	-0.37	-1.25	-0.09	0.24	3.08
ECog executive functioning (p) (2)	Cog	1.23	1.22	1.24	1.37	-0.09	0.20	4.05	0.008				

		Intercepts								Slopes							
Variable (Best model fit)	Domain	Estimates				t-tests: group vs. NA				Estimates				t-tests: NA vs. 0, group vs. NA			
		NA	IA	RP	FP	IA	RP	FP	NA	IA	RP	FP	NA	IA	RP	FP	
ECog language (p) (2)	Cog	1.19	1.17	1.26	1.41	-0.16	1.29	<b>6.86</b>	0.006					1.51			
ECog memory (p) (3)	Cog	1.50	1.33	1.35	1.54	-1.06	-1.52	0.67	-0.02	0.004	0.007	0.01	-2.25	0.60	1.43	<b>3.20</b>	
ECog visual spatial (p) (2)	Cog	1.17	1.11	1.17	1.27	-0.69	0.05	<b>3.55</b>	0.01				<b>3.18</b>				
ECog executive functioning (c) (3)	Cog	1.23	1.23	0.09	0.09	-0.03	0.88	1.57	-0.005	-0.03	0.01	0.05	-0.38	-0.58	0.57	<b>3.44</b>	
ECog language (c) (3)	Cog	1.14	1.02	1.13	1.18	-1.05	-0.15	1.07	-0.01	0.002	0.01	0.02	-1.24	0.34	1.47	<b>3.65</b>	
ECog memory (c) (3)	Cog	1.29	1.18	1.21	1.31	-0.75	-0.90	0.53	-0.004	-0.009	0.03	0.04	-0.39	-0.13	1.66	<b>3.79</b>	
ECog visual spatial (c) (3)	Cog	1.22	1.07	1.13	1.23	-1.14	-1.09	0.11	-0.005	-0.005	0.02	0.03	-0.49	0.01	1.40	<b>3.11</b>	

Best model fit = (1) no baseline group differences or group differences over time; (2) baseline group differences but no group differences over time; (3) baseline group differences and group differences over time. Values 2 appear in **bold**; gradient effects appear in italics. NA = normal; IA = intermediate; RP = reduced penetrance; FP = full penetrance; p = participant version; c = companion version; Stroop word = Stroop Color and Word Test – word condition; Stroop color = Stroop Color and Word Test – color condition; Stroop interference = Stroop Color and Word Test – interference condition; SDMT = Symbol Digit Modalities Test; WHODAS = World Health Organization Disability Assessment Schedule 2.0; TMS = total motor score of the Unified Huntington's Disease Rating Scale; BDI = Beck Depression Inventory; SCL-90 obsession = Symptom Checklist 90 – obsessive compulsive subscale; SCL-90 depression = Symptom Checklist 90 – depression subscale; SCL-90 anxiety = Symptom Checklist 90 – anxiety subscale; SCL-90 hostility = Symptom Checklist 90 – hostility subscale; SCL-90 phobic anxiety = Symptom Checklist 90 – phobic anxiety subscale; SCL-90 psychoticism = Symptom Checklist 90 – psychoticism subscale; FrSBe Executive = Frontal Systems Behavioral Scale – executive subscale; FrSBe disinhibition = Frontal Systems Behavioral Scale – disinhibition subscale; FrSBe apathy = Frontal Systems Behavioral Scale – apathy subscale; ECog = Everyday Cognition scale; Cog = cognitive; Imag = imaging; Func = functional; Beh = behavioral.